c) combining *ex vivo* said recipient PMBCs with said population of donor irradiated T cell-depleted mononuclear cells with a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells;

d) expanding said population of recipient suppressor T cells; and

e) administering said recipient suppressor T cells to said recipient.

REMARKS

Claims 4-8 are pending. Claim 2 has been cancelled. Support for new claim 8 is found in original claim 2 and in the specification at page 13, lines 3-6.

As a preliminary matter, claims 4 and 7 are objected to because they depend on canceled claim 1. Claims 4 and 7 have been amended to depend from independent claim 8. Applicant respectfully requests withdrawal of the objection.

Rejections under 35 U.S.C. § 103(a)

Claims 2, 5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/48524 (Horwitz) in view of Garderet et al., 1999, Transplantation, 67:124-130. Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Horwitz in view of Garderet et al. and further in view of Boning et al, 1998, Scand J. Immunol., 50: 612-618, or Dooms et al, 1998, Cytokine Network 9: 169. As all of the cited references involve Horwitz, the response to the rejections has been combined.

The present invention is directed to methods of preventing graft rejection in a recipient following organ transplantation by administering suppressor T cells. The methods comprise the following steps:

1) isolating peripheral mononuclear blood cells (PMBCs) from a recipient and an organ donor;

2) obtaining a population of donor irradiated T cell-depleted mononuclear cells from said organ donor PMBCs;

3) combining *ex vivo* said recipient PMBCs with said population of irradiated donor T cell-depleted mononuclear cells with a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells;

4) expanding said population of recipient suppressor T cells; and

5) administering said recipient suppressor T cells to said recipient.

See specification at page 8, lines 7-14.

Applicant respectfully submits that the Examiner has mischaracterized Horwitz as Horwitz does not teach mixing irradiated donor and recipient PMBCs ex vivo. Horwitz teaches a method for preventing graft versus host disease (GVHD). The method comprises isolating peripheral mononuclear blood cells (PMBCs) from a donor, combining the donor PMBCs with a population of **irradiated recipient PMBC cells** in the presence of a composition comprising TGF-β to induce a population of **donor suppressor T cells**, and administering the donor suppressor T cells to the recipient. Notably, Horwtiz does not teach, disclose or suggest a method wherein the recipient PBMCs are combined with a population of irradiated donor T cell-

depleted mononuclear cells. Thus, Horwitz does not teach this distinguishing and important step. Moreover, none of the other references of record cure this defect.

Garderet et al., 1999, Transplantation, 67: 124-130, teach a method for separating reactive donor T cells from non-reactive donor T cells to reduce the risk of GVHD. Thus, Garderet et al., teach a method for reducing the risk of GVHD comprising the removal of reactive donor T cells. The disclosure of Garderet et al., does not teach or disclose a method comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells.

Bonig et al., teach methods of overcoming the immunosuppressive effects of TFG-β produced by tumors using cytokines. Thus, the methods taught by Bonig et al., are directed toward using cytokines as means of stimulating the immune response against tumors by neutralizing the effect of immunosuppressive mediators, such as TGF-β. The disclosure of Bonig et al., does not teach or disclose a method comprising incubating recipient PBMCs with a population of donor irradiated T cell-depleted mononuclear cells.

Dooms et al., describe the effects of IL-2 and IL-15 on T cell survival and proliferation. Specifically, Dooms et al., teach that treatment of T cells with IL-2 sensitizes the treated T cells to Fas/Apo-induced cell death, whereas treatment of T cells with IL-15 results in T cell survival, but not cell proliferation. Dooms et al., do not teach or disclose a method comprising incubating recipient PBMCs with a population of donor irradiated T cell-depleted mononuclear cells.

Thus, Applicant submits that the prior art of record, either alone or in combination, does not teach or suggest every limitation of the pending claims as none of the references teach or

disclose a method comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz, in view of Garderet, and further in view of Early et al., 1999, Clin. Exp. Immunol., 116: 527-33, Heitger et al., 1997, Blood, 90: 850-57, and Chen et al., 1998, J. Immunology, 161:909-918.

Horwitz, Garderet and the present invention have been discussed above.

Applicant respectfully submits that the Examiner has mischaracterized Early et al., as Early et al., does not teach a method for enriching naïve CD4+ T cells for reducing the incidence of GVHD. Rather, Early et al., teach methods for understanding the immunocompetence of newborn T cells. Thus, Early et al., does not teach, disclose, or suggest a method to decrease organ rejection comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells.

Heitger et al., teach methods for studying the role of the thymus in the human regeneration of CD4+/CD45RA+ and CD8+/CD45RA+ T cells following bone marrow transplant in humans. Notably, Heitger et al., does not teach, disclose or suggest a method to decrease organ rejection comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells.

Chen et al., teach methods for examining donor T cell immunity to host hemopoietic differentiation antigens as a possible means for using donor T cell responses to host hemopoietic differentiation antigens to eliminate residual host leukemia following bone marrow transplant.

Chen et al., does not teach, disclose or suggest a method to decrease organ rejection comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells.

Thus, Applicant submits that the prior art of record, either alone or in combination, does not teach or suggest every limitation of the pending claims as none of the references teach or disclose a method comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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